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Active Ingredient Search Results from "Rx" table for query on "tacrolimus."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050708		No	TACROLIMUS	Capsule; Oral	EQ 0.5MG BASE	PROGRAF	FUJISAWA HLTHCARE
050708		No	TACROLIMUS	Capsule; Oral	EQ 1MG BASE	PROGRAF	FUJISAWA HLTHCARE
050708		Yes	TACROLIMUS	Capsule; Oral	EQ 5MG BASE	PROGRAF	FUJISAWA HLTHCARE
050709		Yes	TACROLIMUS	Injectable; Injection	EQ 5MG BASE/ML	PROGRAF	FUJISAWA HLTHCARE
050777		No	TACROLIMUS	Ointment; Topical	0.03%	PROTOPIC	FUJISAWA HLTHCARE
050777		Yes	TACROLIMUS	Ointment; Topical	0.1%	PROTOPIC	FUJISAWA HLTHCARE

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PROPOSED PACKAGE INSERT

Revised: January 2001

Prograf®

tacrolimus capsules

tacrolimus injection ***(for intravenous infusion only)***

WARNING

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION:

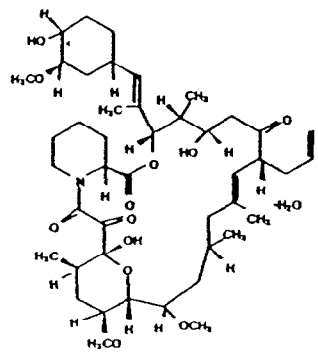
Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell

contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide.

Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.

Tacrolimus, previously known as FK506, is the active ingredient in Prograf. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}\cdot H_2O$ and a formula weight of 822.05. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

CLINICAL PHARMACOLOGY:

Mechanism of Action

Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb.

In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen- induced arthritis, experimental allergic encephalomyelitis, and graft versus host disease.

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

Pharmacokinetics

Tacrolimus activity is primarily due to the parent drug. The pharmacokinetic parameters (mean• S.D.) of tacrolimus have been determined following intravenous (IV) and oral (PO) administration in healthy volunteers, and in kidney transplant and liver transplant patients. (See table below.)

Population	N	Route (Dose)	Parameters					
			C_{max} (ng/mL)	T_{max} (hr)	AUC (ng•hr/mL)	$t_{1/2}$ (hr)	Cl (L/hr/kg)	V (L/kg)
Healthy Volunteers	8	IV (0.025 mg/kg/4hr)	--	--	598* • 125	34.2 • 7.7	0.040 • 0 009	1.91 • 0.31
	16	PO (5 mg)	29 7 • 7.2	1.6 • 0.7	243** • 73	34.8 • 11.4	0.041• • 0.008	1.94• • 0.53
Kidney Transplant Pts	26	IV (0.02 mg/kg/12hr)	--	--	294*** • 262	18.8 • 16.7	0.083 • 0.050	1.41 • 0 66
		PO (0.2 mg/kg/day)	19.2 • 10.3	3.0	203*** • 42	#	#	#
		PO (0 3 mg/kg/day)	24.2 • 15.8	1.5	288*** • 93	#	#	#
Liver Transplant Pts	17	IV (0.05 mg/kg/12 hr)	--	--	3300*** • 2130	11.7 • 3.9	0.053 • 0.017	0.85 • 0 30
		PO (0.3 mg/kg/day)	68.5 • 30.0	2.3 • 1.5	519*** • 179	#	#	#

• Corrected for individual bioavailability
* $AUC_{0\text{-}120}$
** $AUC_{0\text{-}72}$
*** $AUC_{0\text{-}inf}$
-- not applicable
not available

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. (See **DOSAGE AND ADMINISTRATION**).

PROPOSED PACKAGE INSERT

116 Pharmacokinetic data indicate that whole

blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus pharmacokinetics.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17• 10% in adult kidney transplant patients (N=26), 22• 6% in adult liver transplant patients (N=17), and 18• 5% in healthy volunteers (N=16).

A single dose study conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg capsules. Tacrolimus maximum blood concentration (C_{max}) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7 and 10 mg.

In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30 ng/mL measured at 10-12 hours post-dose (C_{min}) correlated well with the AUC (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94.

Food Effects: The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers.

The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean C_{max} by 28% and 65%, respectively.

In healthy volunteers (N=16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.

In 11 liver transplant patients, Prograf administered 15 minutes after a high fat (400 kcal, 34% fat) breakfast, resulted in decreased AUC (27• 18%) and C_{max} (50• 19%), as compared to a fasted state.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. study, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation in vitro. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

The mean clearance following IV administration of tacrolimus is 0.040, 0.083 and 0.053 L/hr/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8• 12.7%. Fecal elimination accounted for 92.4• 1.0% and the elimination half-life based on radioactivity was 48.1• 15.9 hours whereas it was 43.5• 11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029• 0.015 L/hr/kg and clearance of tacrolimus was 0.029• 0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel was 94.9• 30.7%. Fecal elimination accounted for 92.6• 30.7%, urinary elimination accounted for 2.3• 1.1% and the elimination half-life based on radioactivity was 31.9• 10.5 hours whereas it was 48.4• 12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226• 0.116 L/hr/kg and clearance of tacrolimus 0.172• 0.088 L/hr/kg.

Special Populations

Pediatric

Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5• 3.8 hours, 2.6• 2.1 L/kg and 0.138• 0.071 L/hr/kg, respectively. Following oral administration to 9 patients, mean AUC and C_{max} were 337• 167 ng• hr/mL and 43.4• 27.9 ng/mL, respectively. The absolute bioavailability was 31• 21%.

Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations. **(See DOSAGE AND ADMINISTRATION).**

Renal and Hepatic Insufficiency

The mean pharmacokinetic parameters for tacrolimus following single administrations to patients with renal and hepatic impairment are given in the following table.

Population (No. of Patients)	Dose	AUC_{0-t} (ng•hr/mL)	$t_{1/2}$ (hr)	V (L/kg)	Cl (L/hr/kg)
Renal Impairment (n=12)	0.02 mg/kg/4hr IV	393±123 (t=60 hr)	26.3±9.2	1.07 ±0.20	0.038 ±0.014
Mild Hepatic Impairment (n=6)	0.02 mg/kg/4hr IV	367±107 (t=72 hr)	60.6±43.8 Range: 27.8 – 141	3.1 ±1.6	0.042 ±0.02
	7.7 mg PO	488±320 (t=72 hr)	66.1±44.8 Range: 29.5 – 138	3.7 ±4.7*	0.034 ±0.019*
Severe Hepatic Impairment (n=6, IV)	0.02 mg/kg/4hr IV (n=2)	762±204 (t=120 hr)	198±158 Range: 81-436		
	0.01 mg/kg/8hr IV (n=4)	289±117 (t=144 hr)		3.9±1.0	0.017±0.013
(n=5, PO)†	8 mg PO (n=1)	658 (t=120 hr)	119±35 Range: 85-178	3.1±3 4*	0.016±0.011*
	5 mg PO (n=4)	533±156 (t=144 hr)			
	4 mg PO (n=1)				

* corrected for bioavailability

† 1 patient did not receive the PO dose

Renal Insufficiency:

Tacrolimus pharmacokinetics following a single IV administration were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9• 1.6 and 12.0• 2.4 mg/dl., respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups.

The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers (see previous table).

Hepatic Insufficiency:

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see previous table). Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score:>10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration.

Race

A formal study to evaluate the pharmacokinetic disposition of tacrolimus in Black transplant patients has not been conducted. However, a retrospective comparison of Black and Caucasian kidney transplant patients indicated that Black patients required higher tacrolimus doses to attain similar trough concentrations. **(See DOSAGE AND ADMINISTRATION).**

Gender

A formal study to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney and liver transplant patients indicated no gender-based differences.

Clinical Studies

Liver Transplantation

The safety and efficacy of Prograf-based immunosuppression following orthotopic liver transplantation were assessed in two prospective, randomized, non-blinded multicenter studies. The active control groups were treated with a cyclosporine-based immunosuppressive regimen. Both studies used concomitant adrenal corticosteroids as part of the immunosuppressive regimens. These studies were designed to evaluate whether the two regimens were therapeutically equivalent, with patient and graft survival at 12 months following transplantation as the primary endpoints. The Prograf-based immunosuppressive regimen was found to be equivalent to the cyclosporine-based immunosuppressive regimens.

In one trial, 529 patients were enrolled at 12 clinical sites in the United States; prior to surgery, 263 were randomized to the Prograf-based immunosuppressive regimen and 266 to a cyclosporine-based immunosuppressive regimen (CBIR). In 10 of the 12 sites, the same CBIR protocol was used, while 2 sites used different control protocols. This trial excluded patients with renal dysfunction, fulminant hepatic failure with Stage IV encephalopathy, and cancers; pediatric patients (≤ 12 years old) were allowed.

In the second trial, 545 patients were enrolled at 8 clinical sites in Europe; prior to surgery, 270 were randomized to the Prograf-based immunosuppressive regimen and 275 to CBIR. In this study, each center used its local standard CBIR protocol in the active-control arm. This trial excluded pediatric patients, but did allow enrollment of subjects with renal dysfunction, fulminant hepatic failure in Stage IV encephalopathy, and cancers other than primary hepatic with metastases.

One-year patient survival and graft survival in the Prograf-based treatment groups were equivalent to those in the CBIR treatment groups in both studies. The overall one-year patient survival (CBIR and Prograf-based treatment groups combined) was 88% in the U.S. study and 78% in the European study.

The overall one-year graft survival (CBIR and Prograf-based treatment groups combined) was 81% in the U.S. study and 73% in the European study. In both studies, the median time to convert from IV to oral Prograf dosing was 2 days.

Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

Kidney Transplantation

Prograf-based immunosuppression following kidney transplantation was assessed in a Phase III randomized, multicenter, non-blinded, prospective study. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine $\leq$ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

There were 205 patients randomized to Prograf-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids and azathioprine.

Overall one year patient and graft survival was 96.1% and 89.6%, respectively and was equivalent between treatment arms.

Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

INDICATIONS AND USAGE:

Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for patients unable to take Prograf capsules orally.

CONTRAINDICATIONS:

Prograf is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf injection is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil).

WARNINGS:

(See boxed **WARNING.**)

Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney transplant patients

without pretransplant history of diabetes mellitus in the Phase III study (See Tables Below). The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at two years post transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney Transplant Recipients in the Phase III Study

Status of PTDM*	Prograf	CBIR
Patients without pretransplant history of diabetes mellitus.	151	151
New onset PTDM*, 1st Year	30/151 (20%)	6/151 (4%)
Still insulin dependent at one year in those without prior history of diabetes.	25/151(17%)	5/151 (3%)
New onset PTDM* post 1 year	1	0
Patients with PTDM* at 2 years	16/151 (11%)	5/151 (3%)

***use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.**

Development of Post Transplant Diabetes Mellitus by Race and by Treatment Group during First Year Post Kidney Transplantation in the Phase III Study

Patient Race	Prograf		CBIR	
	No. of Patients at Risk	Patients Who Developed PTDM*	No. of Patients At Risk	Patients Who Developed PTDM*
Black	41	15 (37%)	36	3 (8%)
Hispanic	17	5 (29%)	18	1 (6%)
Caucasian	82	10 (12%)	87	1 (1%)
Other	11	0 (0%)	10	1 (10%)
Total	151	30 (20%)	151	6 (4%)

* use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.

Insulin-dependent post-transplant diabetes mellitus was reported in 18% and 11% of Prograf-treated liver transplant patients and was reversible in 45% and 31% of these patients at one year post transplant, in the U.S. and European randomized studies, respectively (See Table below). Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver transplant recipients in the U.S. and European randomized studies, respectively, and may require treatment (see **ADVERSE REACTIONS**).

Incidence of Post Transplant Diabetes Mellitus and Insulin Use at One Year in Liver Transplant Recipients

Status of PTDM*	US Study		European Study	
	Prograf	CBIR	Prograf	CBIR
Patients at risk **	239	236	239	249
New Onset PTDM*	42 (18%)	30 (13%)	26 (11%)	12(5%)
Patients still on insulin at 1 year	23 (10%)	19 (8%)	18 (8%)	6 (2%)

*** use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.**

****Patients without pretransplant history of diabetes mellitus.**

Prograf can cause neurotoxicity and nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively (see **ADVERSE REACTIONS**). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs. **In particular, to avoid excess nephrotoxicity, Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed.**

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with Prograf in the U.S. and European randomized trials, respectively, and may require treatment (see **ADVERSE REACTIONS**). **Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during Prograf therapy (see PRECAUTIONS).**

Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in Prograf-treated kidney transplant patients (54%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant patients was similar in the two treatment groups (see **ADVERSE REACTIONS**). Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving Prograf (see **ADVERSE REACTIONS**). Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

As in patients receiving other immunosuppressants, patients receiving Prograf are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to Prograf following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

A few patients receiving Prograf injection have experienced anaphylactic reactions. Although the exact cause of these reactions is not known, other drugs with castor oil derivatives in the formulation have been associated with anaphylaxis in a small percentage of patients. Because of this potential risk of anaphylaxis, Prograf injection should be reserved for patients who are unable to take Prograf capsules.

Patients receiving Prograf injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped. An aqueous solution of epinephrine should be available at the bedside as well as a source of oxygen.

PRECAUTIONS:

General

Hypertension is a common adverse effect of Prograf therapy (see **ADVERSE REACTIONS**). Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating Prograf-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction (see ***Drug Interactions***).

Renally and Hepatically Impaired Patients

For patients with renal insufficiency some evidence suggests that lower doses should be used (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

The use of Prograf in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole-blood levels of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients (see **DOSAGE AND ADMINISTRATION**).

Myocardial Hypertrophy

Myocardial hypertrophy has been reported in association with the administration of Prograf, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In a group of 20 patients with pre- and post-treatment echocardiograms who showed evidence of myocardial hypertrophy, mean tacrolimus

whole blood concentrations during the period prior to diagnosis of myocardial hypertrophy ranged from 11 to 53 ng/mL in infants (N=10, age 0.4 to 2 years), 4 to 46 ng/mL in children (N=7, age 2 to 15 years) and 11 to 24 ng/mL in adults (N=3, age 37 to 53 years).

In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving Prograf therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of Prograf should be considered.

Information for Patients

Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving Prograf. They should be given complete dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia. Patients should be informed that changes in dosage should not be undertaken without first consulting their physician.

Patients should be informed that Prograf can cause diabetes mellitus and should be advised of the need to see their physician if they develop frequent urination, increased thirst or hunger.

Laboratory Tests

Serum creatinine, potassium, and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

Drug Interactions

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering Prograf with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the co-administration of Prograf and cyclosporine resulted in additive/synergistic nephrotoxicity. Patients switched from cyclosporine to Prograf should receive the first Prograf dose no sooner than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

Drugs that May Alter Tacrolimus Concentrations

Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus as indicated by increased whole blood or plasma concentrations. Drugs known

to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

Drugs That May Increase Tacrolimus Blood Concentrations:

Calcium Channel Blockers	**Antifungal Agents**	**Macrolide Antibiotics**
diltiazem	clotrimazole	clarithromycin
nicardipine	fluconazole	erythromycin
nifedipine	itraconazole	troleandomycin
verapamil	ketoconazole	

Gastrointestinal Prokinetic Agents	**Other Drugs**
cisapride	bromocriptine
metoclopramide	cimetidine
	cyclosporine
	danazol
	ethinyl estradiol
	methylprednisolone
	omeprazole
	protease inhibitors
	nefazodone

In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole administration was significantly decreased

compared to tacrolimus alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV clearance of tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.

Drugs That May Decrease Tacrolimus Blood Concentrations:

Anticonvulsants	Antibiotics
carbamazepine	rifabutin
phenobarbital	rifampin
phenytoin	

Herbal Preparations
St. John's Wort

*This table is not all inclusive

St. John's Wort (hypericum perforatum) induces CYP3A4 and P-glycoprotein. Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving Prograf could result in reduced tacrolimus levels.

In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14±6% vs. 7±3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036±0.008 L/hr/kg vs. 0.053±0.010 L/hr/kg) with concomitant rifampin administration.

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., ritonavir) are administered concomitantly with tacrolimus. Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided **(See DOSAGE AND ADMINISTRATION).**

Other Drug Interactions

Immunosuppressants may affect vaccination. Therefore, during treatment with Prograf, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid.[1]

Carcinogenesis, Mutagenesis and Impairment of Fertility

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin. As with other immunosuppressive therapies, the risk of malignancies in Prograf recipients may be higher than in the normal, healthy

population. Lymphoproliferative disorders associated with Epstein-Barr Virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) in vitro assays of mutagenicity, the in vitro CHO/HGPRT assay of mutagenicity, or in vivo clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Carcinogenicity studies were carried out in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found. The highest doses used in the mouse and rat studies were 0.8 - 2.5 times (mice) and 3.5 - 7.1 times (rats) the recommended clinical dose range of 0.1 - 0.2 mg/kg/day when corrected for body surface area.

No impairment of fertility was demonstrated in studies of male and female rats. Tacrolimus, given orally at 1.0 mg/kg

(0.7 - 1.4X the recommended clinical dose range of 0.1 - 0.2 mg/kg/day based on body surface area corrections) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.3 - 4.6X the recommended clinical dose range based on body surface area correction), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

Pregnancy: Category C

In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions; these doses are equivalent to 0.5 - 1X and 1.6 - 3.3X the recommended clinical dose range (0.1 - 0.2 mg/kg) based on body surface area

corrections. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (equivalent to 0.7 - 1.4X and 2.3 - 4.6X the recommended clinical dose range based on body surface area corrections) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights.

No reduction in male or female fertility was evident.

There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Prograf should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus.

Nursing Mothers

Since tacrolimus is excreted in human milk, nursing should be avoided.

Pediatric Patients

Experience with Prograf in pediatric kidney transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using Prograf. Two randomized active-controlled trials of Prograf in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to Prograf-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Prograf to maintain blood trough concentrations of tacrolimus similar to adult patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS:

Liver Transplantation

The principal adverse reactions of Prograf are tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction. These occur with oral and IV administration of Prograf and may respond to a reduction in dosing. Diarrhea was sometimes associated with other gastrointestinal complaints such as nausea and vomiting.

Hyperkalemia and hypomagnesemia have occurred in patients receiving Prograf therapy. Hyperglycemia has been noted in many patients; some may require insulin therapy (see **WARNINGS**).

The incidence of adverse events was determined in two randomized comparative liver transplant trials among 514 patients receiving tacrolimus and steroids and 515 patients receiving a cyclosporine-based regimen (CBIR). The proportion of patients reporting more than one adverse event was 99.8% in the tacrolimus group and 99.6% in the CBIR group. Precautions must be taken when comparing the incidence of adverse events in the U.S. study to that in the European study. The 12-month posttransplant information from the U.S. study and from the European study is presented below. The two studies also included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse events reported in • 15% in tacrolimus patients (combined study results) are presented below for the two controlled trials in liver transplantation:

LIVER TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN • 15% OF PROGRAF-TREATED PATIENTS

	U.S. STUDY (%)		EUROPEAN STUDY (%)	
	Prograf (N=250)	CBIR (N=250)	Prograf (N=264)	CBIR (N=265)
Nervous System				
Headache (See WARNINGS)	64	60	37	26
Tremor (See WARNINGS)	56	46	48	32
Insomnia	64	68	32	23
Paresthesia	40	30	17	17
Gastrointestinal				
Diarrhea	72	47	37	27
Nausea	46	37	32	27
Constipation	24	27	23	21
LFT Abnormal	36	30	6	5
Anorexia	34	24	7	5
Vomiting	27	15	14	11
Cardiovascular				
Hypertension (See PRECAUTIONS)	47	56	38	43
Urogenital				
Kidney Function Abnormal (See WARNINGS)	40	27	36	23
Creatinine Increased (See WARNINGS)	39	25	24	19
BUN Increased (See WARNINGS)	30	22	12	9
Urinary Tract Infection	16	18	21	19
Oliguria	18	15	19	12
Metabolic and Nutritional				
Hyperkalemia (See WARNINGS)	45	26	13	9
Hypokalemia	29	34	13	16
Hyperglycemia (See WARNINGS)	47	38	33	22
Hypomagnesemia	48	45	16	9

Hemic and Lymphatic					
Anemia	47	38	5	1
Leukocytosis	32	26	8	8
Thrombocytopenia	24	20	14	19
Miscellaneous				
Abdominal Pain	59	54	29	22
Pain	63	57	24	22
Fever	48	56	19	22
Asthenia	52	48	11	7
Back Pain	30	29	17	17
Ascites	27	22	7	8
Peripheral Edema	26	26	12	14
Respiratory System				
Pleural Effusion	30	32	36	35
Atelectasis	28	30	5	4
Dyspnea	9	23	5	4
Skin and Appendages				
Pruritus	36	20	15	7
Rash	24	19	10	4

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patient are described under the subsection **Less Frequently Reported Adverse Reactions** below.

Kidney Transplantation

The most common adverse reactions reported were infection, tremor, hypertension, decreased renal function, constipation, diarrhea, headache, abdominal pain and insomnia.

Adverse events that occurred in • 15 % of Prograf-treated kidney transplant patients are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN • 15% OF PROGRAF-TREATED PATIENTS

	Prograf (N=205)	CBIR (N=207)
Nervous System		
Tremor (See WARNINGS)	54	34
Headache (See WARNINGS)	44	38
Insomnia	32	30
Paresthesia	23	16
Dizziness	19	16
Gastrointestinal		
Diarrhea	44	41
Nausea	38	36
Constipation	35	43
Vomiting	29	23
Dyspepsia	28	20
Cardiovascular		
Hypertension (See PRECAUTIONS)	50	52
Chest pain	19	13

Urogenital		
Creatinine increased (See WARNINGS)	45	42
Urinary tract infection	34	35
Metabolic and Nutritional		
Hypophosphatemia	49	53
Hypomagnesemia	34	17
Hyperlipemia	31	38
Hyperkalemia (See WARNINGS)	31	32
Diabetes mellitus (See WARNINGS)	24	9
Hypokalemia	22	25
Hyperglycemia (See WARNINGS)	22	16
Edema	18	19
Hemic and Lymphatic		
Anemia	30	24
Leukopenia	15	17
Miscellaneous		
Infection	45	49
Peripheral edema	36	48
Asthenia	34	30
Abdominal pain	33	31
Pain	32	30
Fever	29	29
Back pain	24	20

Respiratory System		
Dyspnea	22	18
Cough increased	18	15
Musculoskeletal		
Arthralgia	25	24
Skin		
Rash	17	12
Pruritis	15	7

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described under the subsection **Less Frequently Reported Adverse Reactions** shown below.

Less Frequently Reported Adverse Reactions

The following adverse events were reported in the range of 3% to less than 15% incidence in either liver or kidney transplant recipients who were treated with tacrolimus in the Phase 3 comparative trials.

NERVOUS SYSTEM: (see **WARNINGS**) abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, depression, dizziness, emotional lability, encephalopathy, hallucinations, hypertonia, incoordination, myoclonus, nervousness, neuropathy, psychosis, somnolence, thinking

abnormal; SPECIAL SENSES: abnormal vision, amblyopia, ear pain, otitis media, tinnitus; GASTROINTESTINAL: anorexia, cholangitis, cholestatic jaundice, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gastrointestinal hemorrhage, GGT increase, GI perforation, hepatitis, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, oral moniliasis, rectal disorder, stomatitis; CARDIOVASCULAR: angina pectoris, chest pain, deep thrombophlebitis, abnormal ECG, hemorrhage, hypotension, postural hypotension, peripheral vascular disorder, phlebitis, tachycardia, thrombosis, vasodilatation; UROGENITAL: (see **WARNINGS**) albuminuria, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, pyuria, toxic nephropathy, oliguria, urinary frequency, urinary incontinence, vaginitis; METABOLIC/NUTRITIONAL: acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN increased, dehydration, GGT increased, healing abnormal, hypercalcemia, hypercholesterolemia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic dehydrogenase

increase, weight gain; ENDOCRINE: (see **PRECAUTIONS**) Cushing's syndrome, diabetes mellitus; HEMIC/LYMPHATIC: coagulation disorder, ecchymosis, hypochromic anemia, leukocytosis, leukopenia, polycythemia, prothrombin decreased, serum iron decreased, thrombocytopenia; MISCELLANEOUS: abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills, flu syndrome, generalized edema, hernia, peritonitis, photosensitivity reaction, sepsis; MUSCULOSKELETAL: arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis; RESPIRATORY: asthma, bronchitis, cough increased, lung disorder, pneumothorax, pulmonary edema, pharyngitis, pneumonia, respiratory disorder, rhinitis, sinusitis, voice alteration; SKIN: acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

The overall safety profile of the Prograf-mycophenolate mofetil Phase IV study did not differ from the safety profile of the Phase III kidney study.

Post Marketing

The following have been reported: increased amylase including pancreatitis, hearing loss including deafness, leukoencephalopathy, thrombocytopenic purpura, hemolytic-uremic syndrome, acute renal failure, Stevens-Johnson syndrome, stomach ulcer, glycosuria, cardiac arrhythmia and gastroenteritis.

There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving Prograf therapy (see **PRECAUTIONS-*Myocardial Hypertrophy***).

OVERDOSAGE:

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Occasionally, acute overdosage has been followed by adverse reactions consistent with those listed in the **ADVERSE REACTIONS** section except in one case where transient urticaria and lethargy were observed. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion.

The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

In acute oral and IV toxicity studies, mortalities were seen at or above the following doses: in adult rats, 52X the recommended human oral dose; in immature rats, 16X the recommended oral dose; and in adult rats, 16X the recommended human IV dose (all based on body surface area corrections).

DOSAGE AND ADMINISTRATION:

Prograf injection (tacrolimus injection)

For IV Infusion Only

NOTE: Anaphylactic reactions have occurred with injectables containing castor oil derivatives. See WARNINGS.

In patients unable to take oral Prograf capsules, therapy may be initiated with Prograf injection. The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. The recommended starting dose of Prograf injection is 0.03-0.05 mg/kg/day as a continuous IV infusion. Adult patients should receive doses at the lower end

of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation. Continuous IV infusion of Prograf injection should be continued only until the patient can tolerate oral administration of Prograf capsules.

Preparation for Administration/Stability

Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a concentration between 0.004 mg/mL and 0.02 mg/mL prior to use. Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a PVC container due to decreased stability and the potential for extraction of phthalates. In situations where more dilute solutions are utilized (e.g., pediatric dosing, etc.), PVC-free tubing should likewise be used to minimize the potential for significant drug adsorption onto the tubing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Due to the chemical instability of tacrolimus in alkaline media, Prograf injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir).

Prograf capsules (tacrolimus capsules)-

Summary of Initial Oral Dosage Recommendations and Typical Whole Blood Trough Concentrations

Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
Adult kidney transplant patients	0.2 mg/kg/day	month 1-3 : 7-20 ng/mL month 4-12 : 5-15 ng/mL
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12 : 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	month 1-12 : 5-20 ng/mL

*Note: two divided doses, q12h

Liver Transplantation

It is recommended that patients initiate oral therapy with Prograf capsules if possible. If IV therapy is necessary, conversion from IV to oral Prograf is recommended as soon as oral therapy can be tolerated. This usually occurs within 2-3 days. The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. In a patient receiving an IV infusion, the first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion. The recommended starting oral dose of Prograf capsules is 0.10-0.15 mg/kg/day administered in two divided daily

doses every 12 hours. Co-administered grapefruit juice has been reported to increase tacrolimus blood trough concentrations in liver transplant patients. (See ***Drugs that May Alter Tacrolimus Concentrations***.)

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower Prograf dosages may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post transplant.

Dosage and typical tacrolimus whole blood trough concentrations are shown in the table above; blood concentration details are described in **Blood Concentration Monitoring:** ***Liver Transplantation*** below.

Kidney Transplantation

The recommended starting oral dose of Prograf is 0.2 mg/kg/day administered every 12 hours in two divided doses. The initial dose of Prograf may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered (as indicated for example by a serum creatinine • 4 mg/dL). Black patients may require higher doses to achieve comparable blood concentrations. Dosage and typical tacrolimus whole blood trough concentrations are shown in the table above; blood concentration details are described in **Blood Concentration Monitoring:** ***Kidney Transplantation*** below.

The data in kidney transplant patients indicate that the Black patients required a higher dose to attain comparable trough concentrations compared to Caucasian patients.

Time After Transplant	Caucasian n=114		Black n=56	
	Dose (mg/kg)	Trough Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (ng/mL)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5
Month 12	0.13	10.1	0.19	11.0

Pediatric Patients

Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations. Therefore, it is recommended that therapy be initiated in pediatric patients at a starting IV dose of 0.03-0.05 mg/kg/day and a starting oral dose of 0.15-0.20 mg/kg/day. Dose adjustments may be required. Experience in pediatric kidney transplantation patients is limited.

Patients with Hepatic or Renal Dysfunction

Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Pugh $\geq$ 10) may require lower doses of Prograf. Close monitoring of blood concentrations is warranted. Due to the potential for nephrotoxicity, patients with renal or hepatic impairment should receive doses at the lowest value of the recommended IV and oral dosing ranges. Further reductions in dose below these ranges may be required. Prograf therapy usually should be delayed up to 48 hours or longer in patients with post-operative oliguria.

Conversion from One Immunosuppressive Regimen to Another

Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours before initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed.

Blood Concentration Monitoring

Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential

aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the posttransplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Two methods have been used for the assay of tacrolimus, a microparticle enzyme immunoassay (MEIA) and an ELISA. Both methods have the same monoclonal antibody for tacrolimus. Comparison of the concentrations in published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage. Samples which are not analyzed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep frozen at -20• C for up to 12 months.

Liver Transplantation

Although there is a lack of direct correlation between tacrolimus concentrations and drug efficacy, data from Phase II and III studies of liver transplant patients have shown an increasing incidence of adverse events with increasing trough blood concentrations. Most patients are stable when trough whole blood concentrations are maintained between 5 to 20 ng/mL. Long term posttransplant patients often are maintained at the low end of this target range.

Data from the U.S. clinical trial show that tacrolimus whole blood concentrations, as measured by ELISA, were most variable during the first week post-transplantation. After this early period, the median trough blood concentrations, measured at intervals from the second week to one year post-transplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.

Therapeutic Drug Monitoring, 1995, Volume 17, Number 6 contains a consensus document and several position papers regarding the therapeutic monitoring of tacrolimus from the 1995 International Consensus Conference on Immunosuppressive Drugs. Refer to these manuscripts for further discussions of tacrolimus monitoring.

Kidney Transplantation

Data from the Phase III study indicates that trough concentrations of tacrolimus in whole blood, as measured by IMx®, were most variable during the first week of dosing. During the first three months, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through one-year.

The relative risk of toxicity is increased with higher trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity.

HOW SUPPLIED:

Prograf capsules (tacrolimus capsules)

0.5 mg

Oblong, light yellow, branded with red "0.5 mg" on the capsule cap and " [f] 607" on the capsule body, supplied in 60-count bottles (NDC 0469-0607-67) and 10 blister cards of 10 capsules (NDC 0469-0607-10), containing the equivalent of 0.5 mg anhydrous tacrolimus.

Prograf capsules (tacrolimus capsules)
1 mg
Oblong, white, branded with red "1 mg" on the capsule cap and " f 7" on the capsule body, supplied in 100-count bottles (NDC 0469-0617-71) and 10 blister cards of 10 capsules (NDC 0469-0617-10), containing the equivalent of 1 mg anhydrous tacrolimus.

Prograf capsules (tacrolimus capsules)
5 mg
Oblong, grayish/red, branded with white "5 mg" on the capsule cap and " f 657" on the capsule body, supplied in 100-count bottles (NDC 0469-0657-71) and 10 blister cards of 10 capsules (NDC 0469-0657-10), containing the equivalent of 5 mg anhydrous tacrolimus.

Store and Dispense
Store at 25°C (77°F); excursions permitted to 15• C-30• C (59• F-86• F) [see USP Controlled Room Temperature].

Prograf injection (tacrolimus injection) 5mg (for IV infusion only)
Supplied as a sterile solution in 1 mL ampules containing the equivalent of 5 mg of anhydrous tacrolimus per mL, in boxes of 10 ampules (NDC 0469-3016-01).

Store and Dispense
Store between 5• C and 25• C (41• F and 77• F).

Rx only

Made in Ireland
for Fujisawa Healthcare, Inc.
Deerfield, IL 60015-2548
by Fujisawa Ireland, Ltd.
Killorglin, Co. Kerry Ireland

REFERENCE:

1. CDC: Recommendations of the Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42(RR-4):1-18.

1/23/01

Patient Information

PROGRAF
(tacrolimus capsules)

Read this important information before you start using PROGRAF [PRO-graf] and each time you refill your prescription. This summary does not take the place of talking with your transplant team.

Talk with your transplant team if you have any questions or want more information

about PROGRAF. You can also visit the Fujisawa Internet site at www.fujisawa.com.

What Is PROGRAF?

PROGRAF is a medicine that slows down the body's immune system. For this reason, it works as an anti-rejection medicine. PROGRAF helps patients who have had a liver or kidney transplant protect their new organ and prevent it from being rejected by the body.

How Does PROGRAF Protect My New Organ?

The body's immune system protects the body against anything that it does not recognize as part of the body. For example, when the immune system detects a virus or bacteria it tries to get rid of it to prevent infection. When a person has a liver or kidney transplant, the immune system does not recognize the new organ as a part of the body and tries to get rid of it, too. This is called "rejection." PROGRAF protects your new organ by slowing down the body's immune system.

Who Should Not Take PROGRAF?

Do not take PROGRAF if you are allergic to any of the ingredients in PROGRAF. The active ingredient is tacrolimus. Ask your doctor or pharmacist about the inactive ingredients.

Tell your transplant team about all your health

conditions, including kidney and/or liver problems. Discuss with your transplant team the use of any other prescription and non-prescription medications, including any herbal or over-the-counter remedies that you may take while on Prograf. In very rare cases you may not be able to take Prograf.

Tell your transplant team if you are pregnant, planning to have a baby or are breastfeeding. Talk with your transplant doctor about possible effects PROGRAF could have on your child. Do not nurse a baby while taking PROGRAF since the medicine will be in the breast milk.

How Should I Take PROGRAF?

PROGRAF can protect your new kidney or liver only if you take the medicine correctly.

Your new organ needs around-the-clock protection so your body does not reject it. The success of your transplant depends a great deal upon how well you help PROGRAF do its job. Here is what you can do to help.

- **Take PROGRAF exactly as prescribed**

  It is important to take PROGRAF capsules exactly as your transplant team tells you to.

  PROGRAF comes in several different strength capsules–0.5 mg, 1 mg and 5 mg. Your transplant team will tell you what dose to take and how often to take it. Your transplant team may adjust your dose until they find what works best for you.

  Never change your dose on your own. Never stop taking PROGRAF even if you are feeling well. However, if you

feel poorly on Prograf, discuss this with your transplant team.

- **Take PROGRAF two times a day, 12 hours apart**

Try to pick times that will be easy for you. For example, if you take your first dose at 7:00 a.m. you should take your second dose at 7:00 p.m. Do not vary the times. You must take PROGRAF at the same times every day. If you decide to take PROGRAF at 7:00 a.m. and 7:00 p.m., take it at these same times every day. This will make sure you always have enough medicine in your body to give your new organ the around-the-clock protection it needs.

- **Take PROGRAF the same way each day**

Some people prefer to take PROGRAF with food to help reduce possible stomach upset. Whether you take PROGRAF with or without food, it is important to take PROGRAF the same way every day. For example, if you take

PROGRAF with food, you should always take it with food. Do not eat grapefruit or drink grapefruit juice in combination with your medicine unless your transplant teams approves. Do not change the way you take this medicine without telling your transplant team, since this could change the amount of protection you get from PROGRAF.

- **Take all your doses**

It is important to take your doses twice a day exactly as prescribed by your doctor. If you miss even two doses, your new liver or kidney could lose the protection it needs to defend itself against rejection by your body.

If you miss one dose, do not try to catch up on your own. Call your transplant team right away for instructions on what to do.

If you travel and change time zones, be sure to ask your transplant team how to adjust your dosage schedule so your new organ does not lose its

protection.

- **Plan ahead so that you do not run out of PROGRAF**

  Make sure you have your prescription for PROGRAF refilled and at home before you need it. Circle the date on a calendar when you need to order your refill. Allow extra time if you receive your medicines through the mail.

Your transplant team will follow your progress and watch for early signs of side effects. This is why you will have blood tests done often after your transplant. On the days you are going to have a blood test to measure the amount of PROGRAF in your body, your transplant team may ask you not to take your morning dose until after the blood sample is taken. Check with your transplant team before skipping this dose.

Can Other Medicines Affect How PROGRAF Works?

Some medicines and alcohol can affect how well PROGRAF works. After you start taking PROGRAF:

- Be sure to tell your transplant team, family doctor, dentist,

pharmacist and any other health care professional treating you the names of **all** the medicines you are taking. This includes PROGRAF as well as all other prescription medicines and non-prescription medicines, natural or herbal remedies, nutritional supplements, and vitamins. This is the only way that your health care team can help prevent drug interactions that could be serious.

- Always check with your transplant team before you start taking any new medicine.

- While you are taking PROGRAF, **do not get any vaccinations without your transplant team's approval.** The vaccination may not work as well as it should.

- Liver transplant patients, including those taking PROGRAF, should not drink alcohol.

What Are the Possible Side Effects of PROGRAF?

Tell your transplant team right away if you think

you might be having a side effect. Your transplant team will decide if it is a medicine side effect or a sign that has nothing to do with the medicine but needs to be treated. Infection or reduced urine can be signs of serious problems that you should discuss with your transplant team.

Your transplant team will also follow your progress and watch for the early signs of any side effects. This is why you will have blood tests done often during the first few months after your transplant. On the days you are going to have a blood test to measure the amount of PROGRAF in your body, your transplant team may ask you not to take your morning dose until after the blood sample is taken. Check with your transplant team before skipping this dose.

For Kidney Transplant Patients:

The most common side effects of PROGRAF for kidney transplant patients are infection, headache, tremors (shaking of the body), diarrhea, constipation, nausea, high blood pressure, changes in the amount of urine, and trouble sleeping.

Less common side effects are abdominal pain (stomach pain), numbness or tingling in your hands or feet; loss of appetite; indigestion or

"upset stomach"; vomiting; urinary tract infections; fever; pain; swelling of the hands, ankles or legs; shortness of breath or trouble breathing; cough; leg cramps; heart "fluttering", palpitations or chest pain; unusual weakness or tiredness; dizziness; confusion; changes in mood or emotions; itchy skin, skin rash, and diabetes.

For Liver Transplant Patients:

The most common side effects of PROGRAF for liver transplant patients are headache, tremors (shaking of the body), diarrhea, high blood pressure, nausea and changes in the amount of urine.

Less common side effects are numbness or tingling in your hands or feet; trouble sleeping; constipation; loss of appetite; vomiting; urinary tract infections; fever; pain (especially in the back or abdomen [stomach area]); swelling of the hands, ankles, legs or abdomen; shortness of breath or trouble breathing; cough; unusual bruising; leg cramps; heart "fluttering" or palpitations; unusual weakness or tiredness; confusion; changes in mood or emotions; itchy skin, and skin rash.

Be sure to tell your transplant team right

away if you notice that you are thirstier than usual, have to urinate more often, have blurred vision or seem to get confused. These may be the early signs of high blood sugar or diabetes.

All anti-rejection medicines, including PROGRAF, suppress your body's immune system. As a result, they may increase your chances of getting infections and some kinds of cancer, including skin and lymph gland cancer (lymphoma). As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high sun protection factor (SPF • 15). However, getting cancer from taking an anti-rejection medicine is not common. Talk with your transplant team about any concerns or questions you have.

How Should I Store PROGRAF?

Store PROGRAF in a dry area at room temperature (77° F/25° C). Do not let the medicine get colder than 59° F (15° C) or hotter than 86°F (30° C). For instance, do not leave PROGRAF in the glove compartment of your car in the summer or winter. Do not keep PROGRAF capsules in a hot or moist place such as the medicine cabinet in the bathroom.

General Advice about Prescription Medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use PROGRAF for a condition for which it was not prescribed. Do not give PROGRAF to other people.

This leaflet summarizes the most important information about PROGRAF. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PROGRAF that is written for health professionals. You can also visit the Fujisawa Internet site at www.fujisawa.com.

Fujisawa logotype
[address, copyright, date, code, etc.]

Active Ingredient Search Results from "Rx" table for query on "mycophen."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050722		Yes	MYCOPHENOLATE MOFETIL	Capsule; Oral	250MG	CELLCEPT	ROCHE PALO
050759		Yes	MYCOPHENOLATE MOFETIL	Suspension; Oral	200MG/ML	CELLCEPT	ROCHE PALO
050723		Yes	MYCOPHENOLATE MOFETIL	Tablet; Oral	500MG	CELLCEPT	ROCHE PALO
050758		Yes	MYCOPHENOLATE MOFETIL HYDROCHLORIDE	Injectable; Injection	500MG/VIAL	CELLCEPT	ROCHE PALO

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Roche

CellCept®
(mycophenolate mofetil capsules)
(mycophenolate mofetil tablets)

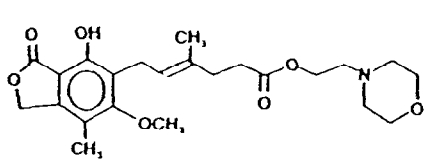
CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)

CellCept® Intravenous
(mycophenolate mofetil hydrochloride for injection)

WARNING: Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should use CellCept. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION: CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula:



Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W). The pH of the reconstituted solution is 2.4 to 4.1.

CellCept® (mycophenolate mofetil)

CellCept is available for oral administration as capsules containing 250 mg of mycophenolate mofetil, tablets containing 500 mg of mycophenolate mofetil, and as a powder for oral suspension, which when constituted contains 200 mg/mL mycophenolate mofetil.

Inactive ingredients in CellCept 250 mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

Inactive ingredients in CellCept 500 mg tablets include black iron oxide, croscarmellose sodium, FD&C blue #2 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone (K-90), red iron oxide, talc, and titanium dioxide; may also contain ammonium hydroxide, ethyl alcohol, methyl alcohol, n-butyl alcohol, propylene glycol, and shellac.

Inactive ingredients in CellCept Oral Suspension include aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin, and xanthan gum.

CellCept Intravenous is the hydrochloride salt of mycophenolate mofetil. The chemical name for the hydrochloride salt of mycophenolate mofetil is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride. It has an empirical formula of $C_{23}H_{31}NO_7$ HCl and a molecular weight of 469.96.

CellCept Intravenous is available as a sterile white to off-white lyophilized powder in vials containing mycophenolate mofetil hydrochloride for administration by intravenous infusion only. Each vial of CellCept Intravenous contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt. The inactive ingredients are polysorbate 80, 25 mg, and citric acid, 5 mg. Sodium hydroxide may have been used in the manufacture of CellCept Intravenous to adjust the pH. Reconstitution and dilution with 5% Dextrose Injection USP yields a slightly yellow solution of mycophenolate mofetil, 6 mg/mL. (For detailed method of preparation, see DOSAGE AND ADMINISTRATION.)

CLINICAL PHARMACOLOGY:

Mechanism of Action: Mycophenolate mofetil has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow).

Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and cardiac allografts in rats, as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies. Mycophenolate mofetil has been demonstrated to inhibit immunologically mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

CellCept® (mycophenolate mofetil)

Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Pharmacokinetics: Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The parent drug, mycophenolate mofetil, can be measured systemically during the intravenous infusion; however, shortly (about 5 minutes) after the infusion is stopped or after oral administration, MMF concentration is below the limit of quantitation (0.4 μg/mL).

Absorption: In 12 healthy volunteers, the mean absolute bioavailability of oral mycophenolate mofetil relative to intravenous mycophenolate mofetil (based on MPA AUC) was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g (see table below on pharmacokinetic parameters).

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g bid to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food (see DOSAGE AND ADMINISTRATION).

Distribution: The mean (±SD) apparent volume of distribution of MPA in 12 healthy volunteers is approximately 3.6 (±1.5) and 4.0 (±1.2) L/kg following intravenous and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed renal graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

CellCept® (mycophenolate mofetil)

In vitro studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with HSA) and MPAG (at ≥460 μg/mL with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide, and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 μg/mL had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

Metabolism: Following oral and intravenous dosing, mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. In vivo, MPAG is converted to MPA via enterohepatic recirculation. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of mycophenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in approximately a 40% decrease in the MPA AUC (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency (see CLINICAL PHARMACOLOGY: *Special Populations*).

Excretion: Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see OVERDOSAGE).

Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration and 16.6 (±5.8) hours and 177 (±31) mL/min following intravenous administration, respectively.

Pharmacokinetics in Healthy Volunteers, Renal, Cardiac, and Hepatic Transplant Patients: Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal, cardiac, and hepatic transplant patients. In the early posttransplant period (<40

days posttransplant), renal, cardiac, and hepatic transplant patients had mean MPA AUCs approximately 20% to 41% lower and mean C_{max} approximately 32% to 44% lower compared to the late transplant period (3 to 6 months posttransplant).

Mean MPA AUC values following administration of 1 g bid intravenous mycophenolate mofetil over 2 hours to renal transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate posttransplant phase. In hepatic transplant patients, administration of 1 g bid intravenous CellCept followed by 1.5 g bid oral CellCept resulted in mean MPA AUC values similar to those found in renal transplant patients administered 1 g CellCept bid.

Pharmacokinetic Parameters for MPA [mean (±SD)] Following Administration of Mycophenolate Mofetil to Healthy Volunteers (Single Dose), Renal, Cardiac, and Hepatic Transplant Patients (Multiple Doses)

	Dose/Route	T_{max} (h)	C_{max} (µg/mL)	Total AUC (µg·h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±16.2) (n=117)
Renal Transplant Patients (bid dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (µg/mL)**	**Interdosing Interval AUC(0-12h) (µg·h/mL)**
5 days	1 g/iv	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1 g/oral	1.33 (±1.05) (n=31)	10.7 (±4.83) (n=31)	32.9 (±15.0) (n=31)
Early (<40 days)	1 g/oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (<40 days)	1.5 g/oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (>3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)
Cardiac Transplant Patients (bid dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (µg/mL)**	**Interdosing Interval AUC(0-12h) (µg·h/mL)**

CellCept® (mycophenolate mofetil)

Early (Day before discharge)	1.5 g/oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=9)
Late (>6 months)	1.5 g/oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1* (±20.4) (n=49)
Hepatic Transplant Patients (bid dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (µg/mL)**	**Interdosing Interval AUC(0-12h) (µg•h/mL)**
4 to 9 days	1 g/iv	1.50 (±0.517) (n=22)	17.0 (±12.7) (n=22)	34.0 (±17.4) (n=22)
Early (5 to 8 days)	1.5 g/oral	1.15 (±0.432) (n=20)	13.1 (±6.76) (n=20)	29.2 (±11.9) (n=20)
Late (>6 months)	1.5 g/oral	1.54 (±0.51) (n=6)	19.3 (±11.7) (n=6)	49.3 (±14.8) (n=6)

** AUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.*

Two 500 mg tablets have been shown to be bioequivalent to four 250 mg capsules. Five mL of the 200 mg/mL constituted oral suspension have been shown to be bioequivalent to four 250 mg capsules.

Special Populations: Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to non-transplant subjects with renal or hepatic impairment.

CellCept® (mycophenolate mofetil)

Pharmacokinetic Parameters for MPA [mean (±SD)] Following Single Doses of Mycophenolate Mofetil Capsules in Chronic Renal and Hepatic Impairment

Renal Impairment (no. of patients)	**Dose**	**T_{max} (h)**	**C_{max} (µg/mL)**	**AUC(0-96h) (µg•h/mL)**
Healthy Volunteers GFR >80 mL/min/1.73 m^2 (n=6)	1 g	0.75 (±0.27)	25.3 (±7.99)	45.0 (±22.6)
Mild Renal Impairment GFR 50 to 80 mL/min/1.73 m^2 (n=6)	1 g	0.75 (±0.27)	26.0 (±3.82)	59.9 (±12.9)
Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 m^2 (n=6)	1 g	0.75 (±0.27)	19.0 (±13.2)	52.9 (±25.5)
Severe Renal Impairment GFR <25 mL/min/1.73 m^2 (n=7)	1 g	1.00 (±0.41)	16.3 (±10.8)	78.6 (±46.4)
Hepatic Impairment (no. of patients)	**Dose**	**T_{max} (h)**	**C_{max} (µg/mL)**	**AUC(0-48h) (µg•h/mL)**
Healthy Volunteers (n=6)	1 g	0.63 (±0.14)	24.3 (±5.73)	29.0 (±5.78)
Alcoholic Cirrhosis (n=18)	1 g	0.85 (±0.58)	22.4 (±10.1)	29.8 (±10.7)

Renal Insufficiency: In a single-dose study, MMF was administered as capsule or intravenous infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73 m^2] was about 75% higher relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 m^2). In addition, the single-dose plasma MPAG AUC was 3-fold to 6-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Plasma MPA AUC observed after single-dose (1 g) intravenous dosing to volunteers (n=4) with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) was 62.4 µg•h/mL (±19.3). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied (see PRECAUTIONS: *General* and DOSAGE AND ADMINISTRATION).

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable to that seen in posttransplant patients without delayed renal graft function. There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. However, dose adjustment does not appear to be necessary in patients with delayed renal graft function. Mean plasma MPAG AUC(0-12h) was 2-fold to 3-fold higher than in posttransplant patients without delayed renal graft function (see PRECAUTIONS: *General* and DOSAGE AND ADMINISTRATION).

CellCept® (mycophenolate mofetil)

In 8 patients with primary graft non-function following renal transplantation, plasma concentrations of MPAG accumulated about 6-fold to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1-fold to 2-fold.

The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (>100 µg/mL), hemodialysis removes only small amounts of MPAG.

Hepatic Insufficiency: In a single-dose (1 g oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies, such as primary biliary cirrhosis, may show a different effect. In a single-dose (1 g intravenous) study of 6 volunteers with severe hepatic impairment (aminopyrine breath test less than 0.2% of dose) due to alcoholic cirrhosis, MMF was rapidly converted to MPA. MPA AUC was 44.1 µg•h/mL (±15.5).

Pediatrics: The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1 year to 18 years of age) receiving CellCept oral suspension at a dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in the following table:

CellCept® (mycophenolate mofetil)

Mean (±SD) Computed Pharmacokinetic Parameters for MPA by Age and Time After Allogeneic Renal Transplantation

Age Group (n)	Time	T_{max} (h)	Dose Adjusted[a] C_{max} (µg/mL)	Dose Adjusted[a] AUC_{0-12} (µg·h/mL)
	Early (Day 7)			
1 to <2 yr (6)[d]		3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
1 to <6 yr (17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to <12 yr (16)		0.940 (0.546)	13.1 (6.30)	33.2 (12.1)
12 to 18 yr (21)		1.16 (0.830)	11.7 (10.7)	26.3 (9.14)[b]
	Late (Month 3)			
1 to <2 yr (4)[d]		0.725 (0.276)	23.8 (13.4)	47.4 (14.7)
1 to <6 yr (15)		0.989 (0.511)	22.7 (10.1)	49.7 (18.2)
6 to <12 yr (14)		1.21 (0.532)	27.8 (14.3)	61.9 (19.6)
12 to 18 yr (17)		0.978 (0.484)	17.9 (9.57)	53.6 (20.3)[c]
	Late (Month 9)			
1 to <2 yr (4)[d]		0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to <6 yr (12)		0.869 (0.479)	30.4 (9.16)	61.0 (10.7)
6 to <12 yr (11)		1.12 (0.462)	29.2 (12.6)	66.8 (21.2)
12 to 18 yr (14)		1.09 (0.518)	18.1 (7.29)	56.7 (14.0)

[a] adjusted to a dose of 600 mg/m^2
[b] n=20
[c] n=16
[d] a subset of 1 to <6 yr

The CellCept oral suspension dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving CellCept capsules at a dose of 1 g bid in the early posttransplant period. There was wide variability in the data. As observed in adults, early posttransplant MPA AUC values were approximately 45% to 53% lower than those observed in the later posttransplant period (>3 months). MPA AUC values were similar in the early and late posttransplant period across the 1 year to 18 year age range.

Gender: Data obtained from several studies were pooled to look at any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (±SD) MPA AUC(0-12h) for males (n=79) was 32.0 (±14.5) and for females (n=41) was 36.5 (±18.8) µg·h/mL while mean (±SD) MPA C_{max} was 9.96 (±6.19) in the males and 10.6 (±5.64) µg/mL in the females. These differences are not of clinical significance.

Geriatrics: Pharmacokinetics in the elderly have not been studied.

CLINICAL STUDIES: The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-

blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients.

Renal Transplant: The three renal studies compared two dose levels of oral CellCept (1 g bid and 1.5 g bid) with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporine (Sandimmune®*) and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®†) induction therapy. These studies are described by geographic location of the investigational sites. One study was conducted in the USA at 14 sites, one study was conducted in Europe at 20 sites, and one study was conducted in Europe, Canada, and Australia at a total of 21 sites.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). CellCept, when administered with antithymocyte globulin (ATGAM®) induction (one study) and with cyclosporine and corticosteroids (all three studies), was compared to the following three therapeutic regimens: (1) antithymocyte globulin (ATGAM®) induction/azathioprine/cyclosporine/corticosteroids, (2) azathioprine/cyclosporine/corticosteroids, and (3) cyclosporine/corticosteroids.

CellCept, in combination with corticosteroids and cyclosporine reduced (statistically significant at 0.05 level) the incidence of treatment failure within the first 6 months following transplantation. The following tables summarize the results of these studies. These tables show (1) the proportion of patients experiencing treatment failure, (2) the proportion of patients who experienced biopsy-proven acute rejection on treatment, and (3) early termination, for any reason other than graft loss or death, without a prior biopsy-proven acute rejection episode. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarized separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients receiving CellCept discontinued without prior biopsy-proven rejection, death or graft loss than discontinued in the control groups, with the highest rate in the CellCept 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in the CellCept 3 g/day group.

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* Sandimmune is a registered trademark of Novartis Pharmaceuticals Corporation.

† ATGAM is a registered trademark of Pharmacia and Upjohn Company.

CellCept® (mycophenolate mofetil)

Renal Transplant Studies
Incidence of Treatment Failure
(Biopsy-proven Rejection or Early Termination for Any Reason)

USA Study† **(N=499 patients)**	**CellCept** **2 g/day** **(n=167 patients)**	**CellCept** **3 g/day** **(n=166 patients)**	**Azathioprine** **1 to 2 mg/kg/day** **(n=166 patients)**
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection*	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%
Europe/Canada/ Australia Study‡ **(N=503 patients)**	**CellCept** **2 g/day** **(n=173 patients)**	**CellCept** **3 g/day** **(n=164 patients)**	**Azathioprine** **100 to 150 mg/day** **(n=166 patients)**
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection*	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study§ **(N=491 patients)**	**CellCept** **2 g/day** **(n=165 patients)**	**CellCept** **3 g/day** **(n=160 patients)**	**Placebo** **(n=166 patients)**
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection*	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

*Does not include death and graft loss as reason for early termination.
†Antithymocyte globulin induction/MMF or azathioprine/cyclosporine/corticosteroids.
‡MMF or azathioprine/cyclosporine/corticosteroids.
§MMF or placebo/cyclosporine/corticosteroids.

The cumulative incidence of 12-month graft loss or patient death is presented below. No advantage of CellCept with respect to graft loss or patient death was established. Numerically, patients receiving CellCept 2 g/day and 3 g/day experienced a better outcome than controls in all three studies; patients receiving CellCept 2 g/day experienced a better outcome than CellCept 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss or patient death at 1 year.

CellCept® (mycophenolate mofetil)

Renal Transplant Studies
Cumulative Incidence of Combined Graft Loss or Patient Death at 12 Months

Study	CellCept 2 g/day	CellCept 3 g/day	Control (Azathioprine or Placebo)
USA	8.5%	11.5%	12.2%
Europe/Canada/Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

Pediatrics: One open-label, safety and pharmacokinetic study of CellCept oral suspension 600 mg/m^2 bid (up to 1 g bid) in combination with cyclosporine and corticosteroids was performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was well tolerated in pediatric patients (see ADVERSE REACTIONS), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bid CellCept capsules (see CLINICAL PHARMACOLOGY: *Pharmacokinetics*). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months posttransplant was similar to that observed in adult renal transplant patients.

Cardiac Transplant: A double-blind, randomized, comparative, parallel-group, multicenter study in primary cardiac transplant recipients was performed at 20 centers in the United States, 1 in Canada, 5 in Europe and 2 in Australia. The total number of patients enrolled was 650; 72 never received study drug and 578 received study drug. Patients received CellCept 1.5 g bid (n=289) or azathioprine 1.5 to 3 mg/kg/day (n=289), in combination with cyclosporine (Sandimmune® or Neoral®*) and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with hemodynamic compromise, or were retransplanted or died, within the first 6 months, and (2) the proportion of patients who died or were retransplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

(1) Rejection: No difference was established between CellCept and azathioprine (AZA) with respect to biopsy-proven rejection with hemodynamic compromise.

(2) Survival. CellCept was shown to be at least as effective as AZA in preventing death or retransplantation at 1 year (see table below).

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* Neoral is a registered trademark of Novartis Pharmaceuticals Corporation.

CellCept® (mycophenolate mofetil)

Rejection at 6 Months/
Death or Retransplantation at 1 Year

	All Patients		Treated Patients	
	AZA N = 323	CellCept N = 327	AZA N = 289	CellCept N = 289
Biopsy-proven rejection with hemodynamic compromise at 6 months*	121 (38%)	120 (37%)	100 (35%)	92 (32%)
Death or retransplantation at 1 year	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)

* Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥20 mm or a 25% increase; cardiac index <2.0 L/min/m^2 or a 25% decrease; ejection fraction ≤30%; pulmonary artery oxygen saturation ≤60% or a 25% decrease; presence of new S_3 gallop; fractional shortening was ≤20% or a 25% decrease; inotropic support required to manage the clinical condition.

Hepatic Transplant: A double-blind, randomized, comparative, parallel-group, multicenter study in primary hepatic transplant recipients was performed at 16 centers in the United States, 2 in Canada, 4 in Europe and 1 in Australia. The total number of patients enrolled was 565. Per protocol, patients received CellCept 1 g bid intravenously for up to 14 days followed by CellCept 1.5 g bid orally or azathioprine 1 to 2 mg/kg/day intravenously followed by azathioprine 1 to 2 mg/kg/day orally, in combination with cyclosporine (Neoral®) and corticosteroids as maintenance immunosuppressive therapy. The actual median oral dose of azathioprine on study was 1.5 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) initially and 1.26 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) at 12 months. The two primary endpoints were: (1) the proportion of patients who experienced, in the first 6 months posttransplantation, one or more episodes of biopsy-proven and treated rejection or death or retransplantation, and (2) the proportion of patients who experienced graft loss (death or retransplantation) during the first 12 months posttransplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death or retransplantation) for 1 year.

Results: In combination with corticosteroids and cyclosporine, CellCept obtained a lower rate of acute rejection at 6 months and a similar rate of death or retransplantation at 1 year compared to azathioprine.

CellCept® (mycophenolate mofetil)

	Rejection at 6 Months/ Death or Retransplantation at 1 Year	
	AZA N = 287	CellCept N = 278
Biopsy-proven, treated rejection at 6 months (includes death or retransplantation)	137 (47.7%)	107 (38.5%)
Death or retransplantation at 1 year	42 (14.6%)	41 (14.7%)

INDICATIONS AND USAGE: ***Renal, Cardiac, and Hepatic Transplant:*** CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

CONTRAINDICATIONS: Allergic reactions to CellCept have been observed; therefore, CellCept is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. CellCept Intravenous is contraindicated in patients who are allergic to Polysorbate 80 (TWEEN).

WARNINGS (see boxed WARNING): Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see ADVERSE REACTIONS). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

CellCept has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM®), OKT3 (Orthoclone OKT® 3*), cyclosporine (Sandimmune®, Neoral®) and corticosteroids. The efficacy and safety of the use of CellCept in combination with other immunosuppressive agents have not been determined.

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* Orthoclone OKT is a registered trademark of Ortho Biotech Inc.

CellCept® (mycophenolate mofetil)

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients (see ADVERSE REACTIONS).

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed (see ADVERSE REACTIONS).

Adverse effects on fetal development (including malformations) occurred when pregnant rats and rabbits were dosed during organogenesis. These responses occurred at doses lower than those associated with maternal toxicity, and at doses below the recommended clinical dose for renal, cardiac or hepatic transplantation. There are no adequate and well-controlled studies in pregnant women. However, as CellCept has been shown to have teratogenic effects in animals, it may cause fetal harm when administered to a pregnant woman. Therefore, CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is recommended that CellCept therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

Effective contraception must be used before beginning CellCept therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method (see PRECAUTIONS: *Drug Interactions*). If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy (see PRECAUTIONS: *Pregnancy* and *Information for Patients*).

In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see ADVERSE REACTIONS).

Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu L$] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving CellCept 3 g daily (see ADVERSE REACTIONS). Patients receiving CellCept should be monitored for neutropenia (see PRECAUTIONS: *Laboratory Tests*). The development of neutropenia may be related to CellCept itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC $<1.3 \times 10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION). Neutropenia has been observed most frequently in the period from 31 to 180 days posttransplant in patients treated for prevention of renal, cardiac, and hepatic rejection.

Patients receiving CellCept should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

CellCept® (mycophenolate mofetil)

CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION.

PRECAUTIONS: ***General:*** Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with CellCept 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed.

Gastrointestinal perforations have rarely been observed. Most patients receiving CellCept were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate mofetil. Because CellCept has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, CellCept should be administered with caution in patients with active serious digestive system disease.

Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) who have received single doses of CellCept showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of CellCept greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and DOSAGE AND ADMINISTRATION).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. CellCept may be used for cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable, but MPAG AUC(0-12h) was 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. In the three controlled studies of prevention of renal rejection, there were 298 of 1483 patients (20%) with delayed graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and DOSAGE AND ADMINISTRATION).

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept than in those receiving azathioprine therapy, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept (see ADVERSE REACTIONS).

CellCept® (mycophenolate mofetil)

There were more herpes virus (H. simplex, H. zoster, and cytomegalovirus) infections in cardiac transplant patients treated with CellCept compared to those treated with azathioprine (see ADVERSE REACTIONS).

It is recommended that CellCept not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of CellCept with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of CellCept (see PRECAUTIONS: *Drug Interactions*).

On theoretical grounds, because CellCept is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

During treatment with CellCept, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see PRECAUTIONS: *Drug Interactions: Live Vaccines*).

Phenylketonurics: CellCept Oral Suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/mL suspension). Therefore, care should be taken if CellCept Oral Suspension is administered to patients with phenylketonuria.

Information for Patients: Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving CellCept. Patients should be given complete dosage instructions and informed of the increased risk of lymphoproliferative disease and certain other malignancies. Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning CellCept therapy, during therapy, and for 6 weeks after CellCept has been stopped (see WARNINGS and PRECAUTIONS: *Pregnancy*).

Laboratory Tests: Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year (see WARNINGS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Drug Interactions: Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, and trimethoprim/sulfamethoxazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal, cardiac or hepatic transplant patients. CellCept has not been administered concomitantly with azathioprine.

CellCept® (mycophenolate mofetil)

Acyclovir: Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and C_{max}. However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for the two drugs to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids With Magnesium and Aluminum Hydroxides: Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when administered to ten rheumatoid arthritis patients also taking Maalox®* TC (10 mL qid). The C_{max} and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when mycophenolate mofetil was administered alone under fasting conditions. CellCept may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that CellCept and the antacid not be administered simultaneously.

Cholestyramine: Following single-dose administration of 1.5 g mycophenolate mofetil to 12 healthy volunteers pretreated with 4 g tid of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of CellCept. Therefore, CellCept is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Cyclosporine: Cyclosporine (Sandimmune®) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10 stable renal transplant patients. The mean (±SD) AUC(0-12h) and C_{max} of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 (±822) ng•h/mL and 753 (±161) ng/mL, respectively, compared to 3245 (±1088) ng•h/mL and 700 (±246) ng/mL, respectively, 1 week before administration of mycophenolate mofetil. The effect of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in this study; however, plasma concentrations of MPA were similar to that for healthy volunteers.

Ganciclovir: Following single-dose administration to 12 stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and C_{max} (n=10) were 54.3 (±19.0) µg•h/mL and 11.5 (±1.8) µg/mL, respectively, after coadministration of the two drugs, compared to 51.0 (±17.0) µg•h/mL and 10.6 (±2.0) µg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (±SD) AUC and C_{max} of MPA (n=12) after coadministration were 80.9 (±21.6) µg•h/mL and 27.8 (±13.9) µg/mL, respectively, compared to values of 80.3 (±16.4) µg•h/mL and 30.9 (±11.2) µg/mL, respectively, after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In

* Maalox is a registered trademark of Novartis Consumer Health, Inc.

patients with renal impairment in which MMF and ganciclovir are coadministered, patients should be monitored carefully.

Oral Contraceptives: A study of coadministration of CellCept (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC(0-24h) significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. CellCept may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. However, it is recommended that oral contraceptives are coadministered with CellCept with caution and additional birth control methods be considered (see PRECAUTIONS: *Pregnancy*).

Trimethoprim/sulfamethoxazole: Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy male volunteers on day 8 of a 10 day course of Bactrim™* DS (trimethoprim 160 mg/sulfamethoxazole 800 mg) administered bid, no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and C_{max} of MPA after concomitant administration were 75.2 (±19.8) μg•h/mL and 34.0 (±6.6) μg/mL, respectively, compared to 79.2 (±27.9) μg•h/mL and 34.2 (±10.7) μg/mL, respectively, after administration of mycophenolate mofetil alone.

Other Interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, coadministration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in monkeys results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

Live Vaccines: During treatment with CellCept, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see PRECAUTIONS: *General*). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the recommended clinical dose (3 g/day) in cardiac transplant patients

* Bactrim is a trademark of Hoffmann-La Roche Inc.

when corrected for differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats, mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk (see WARNINGS).

The genotoxic potential of mycophenolate mofetil was determined in five assays. Mycophenolate mofetil was genotoxic in the mouse lymphoma/thymidine kinase assay and the in vivo mouse micronucleus assay. Mycophenolate mofetil was not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal transplant patients and 0.07 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

Pregnancy: *Category C.* In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day and in rabbits at 90 mg/kg/day, in the absence of maternal toxicity. These levels are equivalent to 0.03 to 0.92 times the recommended clinical dose in renal transplant patients and 0.02 to 0.61 times the recommended clinical dose in cardiac transplant patients on a BSA basis. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

There are no adequate and well-controlled studies in pregnant women. CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. Effective contraception must be used before beginning CellCept therapy, during therapy and for 6 weeks after CellCept has been stopped (see WARNINGS and PRECAUTIONS: *Information for Patients*).

Nursing Mothers: Studies in rats treated with mycophenolate mofetil have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to

discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of CellCept oral suspension is 600 mg/m^2 bid (up to a maximum of 1 g bid). Also see CLINICAL PHARMACOLOGY, CLINICAL STUDIES, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

Safety and effectiveness in pediatric patients receiving allogeneic cardiac or hepatic transplants have not been established.

Geriatric Use: Clinical studies of CellCept did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals (see ADVERSE REACTIONS).

ADVERSE REACTIONS: The principal adverse reactions associated with the administration of CellCept include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection (see WARNINGS). The adverse event profile associated with the administration of CellCept Intravenous has been shown to be similar to that observed after administration of oral dosage forms of CellCept.

CellCept Oral: The incidence of adverse events for CellCept was determined in randomized, comparative, double-blind trials in prevention of rejection in renal (2 active, 1 placebo-controlled trials), cardiac (1 active-controlled trial), and hepatic (1 active-controlled trial) transplant patients.

Elderly patients (≥65 years), particularly those who are receiving CellCept as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus (CMV) tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals (see PRECAUTIONS).

Safety data are summarized below for all active-controlled trials in renal (2 trials), cardiac (1 trial), and hepatic (1 trial) transplant patients. Approximately 53% of the renal patients, 65% of the cardiac patients, and 48% of the hepatic patients have been treated for more than 1 year. Adverse events reported in ≥20% of patients in the CellCept treatment groups are presented below.

CellCept® (mycophenolate mofetil)

Adverse Events in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Allograft Rejection (Reported in ≥20% of Patients in the CellCept Group)

	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept 2 g/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day	CellCept 3 g/day	Azathioprine 1.5 to 3 mg/kg/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day
	(n=336)	(n=330)	(n=326)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Body as a Whole							
Pain	33.0	31.2	32.2	75.8	74.7	74.0	77.7
Abdominal pain	24.7	27.6	23.0	33.9	33.2	62.5	51.2
Fever	21.4	23.3	23.3	47.4	46.4	52.3	56.1
Headache	21.1	16.1	21.2	54.3	51.9	53.8	49.1
Infection	18.2	20.9	19.9	25.6	19.4	27.1	25.1
Sepsis	–	–	–	–	–	27.4	26.5
Asthenia	–	–	–	43.3	36.3	35.4	33.8
Chest pain	–	–	–	26.3	26.0	–	–
Back pain	–	–	–	34.6	28.4	46.6	47.4
Ascites	–	–	–	–	–	24.2	22.6
Hemic and Lymphatic							
Anemia	25.6	25.8	23.6	42.9	43.9	43.0	53.0
Leukopenia	23.2	34.5	24.8	30.4	39.1	45.8	39.0
Thrombocytopenia	–	–	–	23.5	27.0	38.3	42.2
Hypochromic anemia	–	–	–	24.6	23 5	–	–
Leukocytosis	–	–	–	40.5	35.6	22.4	21.3
Urogenital							
Urinary tract infection	37.2	37.0	33.7	–	–	–	–
Kidney function abnormal	–	–	–	21.8	26.3	25.6	28.9
Cardiovascular							
Hypertension	32.4	28.2	32.2	77.5	72.3	62.1	59.6
Hypotension	–	–	–	32.5	36.0	–	–
Cardiovascular disorder	–	–	–	25.6	24.2	–	–
Tachycardia	–	–	–	20.1	18.0	22.0	15.7
Metabolic and Nutritional							
Peripheral edema	28.6	27.0	28.2	64.0	53.3	48.4	47.7
Hyper-cholesteremia	–	–	–	41.2	38.4	–	–
Edema	–	–	–	26 6	25.6	28.2	28.2
Hypokalemia	–	–	–	31.8	25 6	37.2	41.1
Hyperkalemia	–	–	–	–	–	22.0	23.7
Hyperglycemia	–	–	–	46 7	52.6	43.7	48.8

CellCept® (mycophenolate mofetil)

Adverse Events in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Allograft Rejection (Reported in ≥20% of Patients in the CellCept Group)

	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept 2 g/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day	CellCept 3 g/day	Azathioprine 1.5 to 3 mg/kg/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day
	(n=336)	(n=330)	(n=326)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Creatinine increased	–	–	–	39.4	36.0	–	–
BUN increased	–	–	–	34.6	32.5	–	–
Lactic dehydrogenase increased	–	–	–	23.2	17.0	–	–
Hypomagnesemia	–	–	–	–	–	39.0	37.6
Hypocalcemia	–	–	–	–	–	30.0	30.0
Digestive							
Diarrhea	31.0	36.1	20.9	45.3	34.3	51.3	49.8
Constipation	22.9	18.5	22.4	41.2	37.7	37.9	38.3
Nausea	19.9	23.6	24.5	54.0	54.3	54.5	51.2
Dyspepsia	–	–	–	–	–	22.4	20.9
Vomiting	–	–	–	33.9	28.4	32.9	33.4
Anorexia	–	–	–	–	–	25.3	17.1
Liver function tests abnormal	–	–	–	–	–	24.9	19.2
Respiratory							
Infection	22.0	23.9	19.6	37.0	35.3	–	–
Dyspnea	–	–	–	36.7	36.3	31.0	30.3
Cough increased	–	–	–	31.1	25.6	–	–
Lung disorder	–	–	–	30.1	29.1	22.0	18.8
Sinusitis	–	–	–	26.0	19.0	–	–
Pleural effusion	–	–	–	–	–	34.3	35.9
Skin and Appendages							
Rash	–	–	–	22.1	18.0	–	–
Nervous System							
Tremor	–	–	–	24.2	23.9	33.9	35.5
Insomnia	–	–	–	40.8	37.7	52.3	47.0
Dizziness	–	–	–	28.7	27.7	–	–
Anxiety	–	–	–	28.4	23.9	–	–
Paresthesia	–	–	–	20.8	18.0	–	–

The placebo-controlled renal transplant study generally showed fewer adverse events occurring in ≥20% of patients. In addition, those that occurred were not only qualitatively similar to the azathioprine-controlled renal transplant studies, but also occurred at lower rates, particularly for infection, leukopenia, hypertension, diarrhea and respiratory infection.

CellCept® (mycophenolate mofetil)

The above data demonstrate that in three controlled trials for prevention of renal rejection, patients receiving 2 g/day of CellCept had an overall better safety profile than did patients receiving 3 g/day of CellCept.

The above data demonstrate that the types of adverse events observed in multicenter controlled trials in renal, cardiac, and hepatic transplant patients are qualitatively similar except for those that are unique to the specific organ involved.

Sepsis, which was generally CMV viremia, was slightly more common in renal transplant patients treated with CellCept compared to patients treated with azathioprine. The incidence of sepsis was comparable in CellCept and in azathioprine-treated patients in cardiac and hepatic studies.

In the digestive system, diarrhea was increased in renal and cardiac transplant patients receiving CellCept compared to patients receiving azathioprine, but was comparable in hepatic transplant patients treated with CellCept or azathioprine.

Patients receiving CellCept alone or as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see WARNINGS). The incidence of malignancies among the 1483 patients treated in controlled trials for the prevention of renal allograft rejection who were followed for ≥1 year was similar to the incidence reported in the literature for renal allograft recipients.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g daily) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients followed for at least 1 year (see WARNINGS). Non-melanoma skin carcinomas occurred in 1.6% to 4.2% of patients, other types of malignancy in 0.7% to 2.1% of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data.

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed.

Severe neutropenia (ANC $<0.5 \times 10^3/\mu L$) developed in up to 2.0% of renal transplant patients, up to 2.8% of cardiac transplant patients and up to 3.6% of hepatic transplant patients receiving CellCept 3 g daily (see WARNINGS, PRECAUTIONS: *Laboratory Tests* and DOSAGE AND ADMINISTRATION).

All transplant patients are at increased risk of opportunistic infections. The risk increases with total immunosuppressive load (see WARNINGS). The following table shows the incidence of opportunistic infections that occurred in the renal, cardiac, and hepatic transplant populations in the azathioprine-controlled prevention trials:

CellCept® (mycophenolate mofetil)

Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection

	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept 2 g/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day	CellCept 3 g/day	Azathioprine 1.5 to 3 mg/kg/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day
	(n=336)	(n=330)	(n=326)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Herpes simplex	16.7	20.0	19.0	20.8	14.5	10.1	5.9
CMV							
– Viremia/ syndrome	13.4	12.4	13.8	12.1	10.0	14.1	12.2
– Tissue invasive disease	8.3	11.5	6.1	11.4	8.7	5.8	8.0
Herpes zoster	6.0	7.6	5.8	10.7	5.9	4.3	4.9
– Cutaneous disease	6.0	7.3	5.5	10.0	5.5	4.3	4.9
Candida	17.0	17.3	18.1	18.7	17.6	22.4	24.4
– Mucocutaneous	15.5	16.4	15.3	18.0	17.3	18.4	17.4

The following other opportunistic infections occurred with an incidence of less than 4% in CellCept patients in the above azathioprine-controlled studies: Herpes zoster, visceral disease; Candida, urinary tract infection, fungemia/disseminated disease, tissue invasive disease; Cryptococcosis; Aspergillus/Mucor; Pneumocystis carinii.

In the placebo-controlled renal transplant study, the same pattern of opportunistic infection was observed compared to the azathioprine-controlled renal studies, with a notably lower incidence of the following: Herpes simplex and CMV tissue-invasive disease.

In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see WARNINGS).

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept than in those receiving azathioprine, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept.

The following adverse events were reported with 3% to <20% incidence in renal, cardiac, and hepatic transplant patients treated with CellCept, in combination with cyclosporine and corticosteroids.

CellCept® (mycophenolate mofetil)

Adverse Events Reported in 3% to <20% of Patients Treated With CellCept in Combination With Cyclosporine and Corticosteroids

Body System	
Body as a Whole	Abdomen enlarged, abscess, accidental injury, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, lab test abnormal, malaise, neck pain, pelvic pain, peritonitis
Hemic and Lymphatic	coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased
Urogenital	acute kidney failure, albuminuria, dysuria, hydronephrosis, hematuria, impotence, kidney failure, kidney tubular necrosis nocturia, oliguria, pain, prostatic disorder, pyelonephritis, scrotal edema, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder
Cardiovascular	angina pectoris, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiovascular disorder, congestive heart failure, extrasystole, heart arrest, heart failure, hypotension, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, tachycardia, thrombosis, vasodilatation, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased
Metabolic and Nutritional	abnormal healing, acidosis, alkaline phosphatase increased, alkalosis, bilirubinemia, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, generalized edema, gout, hypercalcemia, hypercholesteremia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypochloremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, hypovolemia, hypoxia, lactic dehydrogenase increased, respiratory acidosis, SGOT increased, SGPT increased, thirst, weight gain, weight loss
Digestive	anorexia, cholangitis, cholestatic jaundice, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, jaundice, liver damage, liver function tests abnormal, melena, mouth ulceration, nausea and vomiting, oral moniliasis, rectal disorder, stomach ulcer, stomatitis
Respiratory	apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, lung edema, lung disorder, neoplasm, pain, pharyngitis, pleural effusion, pneumonia, pneumothorax, respiratory disorder, respiratory moniliasis, rhinitis, sinusitis, sputum increased, voice alteration
Skin and Appendages	acne, alopecia, fungal dermatitis, hemorrhage, hirsutism, pruritus, rash, skin benign neoplasm, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, sweating, vesiculobullous rash

CellCept® (mycophenolate mofetil)

Adverse Events Reported in 3% to <20% of Patients Treated With CellCept in Combination With Cyclosporine and Corticosteroids

Body System	
Nervous	agitation, anxiety, confusion, convulsion, delirium, depression, dry mouth, emotional lability, hallucinations, hypertonia, hypesthesia, nervousness, neuropathy, paresthesia, psychosis, somnolence, thinking abnormal, vertigo
Endocrine	Cushing's syndrome, diabetes mellitus, hypothyroidism, parathyroid disorder
Musculoskeletal	arthralgia, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis
Special Senses	abnormal vision, amblyopia, cataract (not specified), conjunctivitis, deafness, ear disorder, ear pain, eye hemorrhage, tinnitus, lacrimation disorder

Pediatrics: The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with CellCept oral suspension 600 mg/m^2 bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with CellCept capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, and anemia, which were observed in a higher proportion in pediatric patients.

CellCept Intravenous: The adverse event profile of CellCept Intravenous was determined from a single, double-blind, controlled comparative study of the safety of 2 g/day of intravenous and oral CellCept in renal transplant patients in the immediate posttransplant period (administered for the first 5 days). The potential venous irritation of CellCept Intravenous was evaluated by comparing the adverse events attributable to peripheral venous infusion of CellCept Intravenous with those observed in the intravenous placebo group; patients in this group received active medication by the oral route.

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with CellCept Intravenous.

In the active controlled study in hepatic transplant patients, 2 g/day of CellCept Intravenous were administered in the immediate posttransplant period (up to 14 days). The safety profile of intravenous CellCept was similar to that of intravenous azathioprine.

Postmarketing Experience

Digestive: colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

Resistance Mechanism Disorders: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher

frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in posttransplant patients receiving CellCept.

OVERDOSAGE: There has been no reported experience of overdosage of mycophenolate mofetil in humans. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 4000 mg/kg or in adult monkeys at doses up to 1000 mg/kg; these were the highest doses of mycophenolate mofetil tested in these species. These doses represent 11 times the recommended clinical dose in renal transplant patients and approximately 7 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In adult rats, deaths occurred after single-oral doses of 500 mg/kg of mycophenolate mofetil. The dose represents approximately 3 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine (see CLINICAL PHARMACOLOGY: *Pharmacokinetics*).

DOSAGE AND ADMINISTRATION: ***RENAL TRANSPLANTATION:***

Adults: A dose of 1 g administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g/day of CellCept demonstrated an overall better safety profile than did patients receiving 3 g/day of CellCept.

Pediatrics: The recommended dose of CellCept oral suspension is 600 mg/m^2 administered twice daily (up to a maximum daily dose of 2 g/10 mL oral suspension). Patients with a body surface area of 1.25 m^2 to 1.5 m^2 may be dosed with CellCept capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area >1.5 m^2 may be dosed with CellCept capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

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CARDIAC TRANSPLANTATION: A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult cardiac transplant patients.

HEPATIC TRANSPLANTATION: A dose of 1 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult hepatic transplant patients.

CellCept Capsules, Tablets, and Oral Suspension: The initial oral dose of CellCept should be given as soon as possible following renal, cardiac or hepatic transplantation. Food had no effect on MPA AUC, but has been shown to decrease MPA C_{max} by 40%. Therefore, it is recommended that CellCept be administered on an empty stomach. However, in stable renal transplant patients, CellCept may be administered with food if necessary.

Note:
If required, CellCept Oral Suspension can be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

Patients With Hepatic Impairment: No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies (see CLINICAL PHARMACOLOGY: *Pharmacokinetics*).

No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Geriatrics: The recommended oral dose of 1 g bid for renal transplant patients, 1.5 g bid for cardiac transplant patients, and 1 g bid administered intravenously or 1.5 g bid administered orally in hepatic transplant patients is appropriate for elderly patients (see PRECAUTIONS: *Geriatric Use*).

Preparation of Oral Suspension

It is recommended that CellCept Oral Suspension be constituted by the pharmacist prior to dispensing to the patient.

CellCept Oral Suspension should not be mixed with any other medication.

Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits. There are no adequate and well-controlled studies in pregnant women. (See WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and HANDLING AND DISPOSAL.) Care should be taken to avoid inhalation or direct contact with skin or mucous membranes of the dry powder or the constituted suspension. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water.

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1. Tap the closed bottle several times to loosen the powder.

2. Measure 94 mL of water in a graduated cylinder.

3. Add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute.

4. Add the remainder of water and shake the closed bottle well for about 1 minute.

5. Remove the child-resistant cap and push bottle adapter into neck of bottle.

6. Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

Dispense with patient instruction sheet and oral dispensers. It is recommended to write the date of expiration of the constituted suspension on the bottle label. (The shelf-life of the constituted suspension is 60 days.)

After constitution the oral suspension contains 200 mg/mL mycophenolate mofetil. Store constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable. Do not freeze. Discard any unused portion 60 days after constitution.

CellCept Intravenous: CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension recommended for patients unable to take oral CellCept. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

CellCept Intravenous must be reconstituted and diluted to a concentration of 6 mg/mL using 5% Dextrose Injection USP. CellCept Intravenous is incompatible with other intravenous infusion solutions. Following reconstitution, CellCept Intravenous must be administered by slow intravenous infusion over a period of NO LESS THAN 2 HOURS by either peripheral or central vein.

CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION (see WARNINGS).

Preparation of Infusion Solution (6 mg/mL)

Caution should be exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid direct contact of the prepared solution of CellCept Intravenous with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. (See WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and HANDLING AND DISPOSAL.)

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CellCept Intravenous does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.

CellCept Intravenous infusion solution must be prepared in two steps: the first step is a reconstitution step with 5% Dextrose Injection USP, and the second step is a dilution step with 5% Dextrose Injection USP. A detailed description of the preparation is given below:

Step 1

a. Two (2) vials of CellCept Intravenous are used for preparing each 1 g dose, whereas three (3) vials are needed for each 1.5 g dose. Reconstitute the contents of each vial by injecting 14 mL of 5% Dextrose Injection USP.

b. Gently shake the vial to dissolve the drug.

c. Inspect the resulting slightly yellow solution for particulate matter and discoloration prior to further dilution. Discard the vials if particulate matter or discoloration is observed.

Step 2

a. To prepare a 1 g dose, further dilute the contents of the two reconstituted vials (approx. 2 x 15 mL) into 140 mL of 5% Dextrose Injection USP. To prepare a 1.5 g dose, further dilute the contents of the three reconstituted vials (approx. 3 x 15 mL) into 210 mL of 5% Dextrose Injection USP. The final concentration of both solutions is 6 mg mycophenolate mofetil per mL.

b. Inspect the infusion solution for particulate matter or discoloration. Discard the infusion solution if particulate matter or discoloration is observed.

If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 4 hours from reconstitution and dilution of the drug product. Keep solutions at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

CellCept Intravenous should not be mixed or administered concurrently via the same infusion catheter with other intravenous drugs or infusion admixtures.

Dosage Adjustments: In renal transplant patients with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) outside the immediate posttransplant period, doses of CellCept greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in renal transplant patients experiencing delayed graft function postoperatively (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and PRECAUTIONS: *General*).